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## Early View

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# **Pulmonary artery pressure at rest and during exercise in Chronic Mountain**

## **Sickness: a meta-analysis**

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## TAKE HOME MESSAGE

This meta-analysis shows that in high-altitude dwellers suffering from chronic mountain sickness pulmonary hypertension, while rare at rest, is frequent during daily activities.

**Keywords:** chronic mountain sickness; echocardiography; meta-analysis; systolic pulmonary artery pressure

## Abstract

Among the >140 million dwellers worldwide up to 10% suffer from chronic mountain sickness (CMS). Patients suffering from this debilitating problem often display increased pulmonary artery pressure (PAP) which may contribute to exercise intolerance and right heart failure. However, there is little information on the usual PAP in these patients.

We systematically reviewed and meta-analyzed all data published in English or Spanish until June 2018 on echocardiographic estimations of PAP at rest and during mild exercise in CMS patients.

Nine studies, comprising 287 participants fulfilled the inclusion criteria. At rest, the point estimate from meta-analysis of the mean systolic PAP was 28.0 mmHg [95% confidence interval (CI) 26.3, 29.6]. These values are 11% (+2.7 mm Hg) higher than those recently meta-analysed in apparently healthy high-altitude dwellers (J Appl Physiol 121:1151–9, 2016). During mild exercise (50 W) the difference in mean systolic PAP between patients and high-altitude dwellers was markedly more accentuated (48.3 vs. 36.3 mm Hg) than at rest.

These findings indicate that in patients with CMS PAP is moderately increased at rest, but markedly increased during mild exercise, which will be common with activities of daily living.

## INTRODUCTION

An increase of pulmonary artery pressure is a hallmark of high-altitude exposure and, if pronounced, it may be associated with important morbidity and mortality. Worldwide more than 140 million people are living at high altitude of whom a substantial number are suffering from chronic mountain sickness (CMS) [1, 2]. For example, among Andean high-altitude dwellers, an estimated 5-10 % are suffering from this debilitating disease characterized by excessive erythrocytosis and arterial hypoxemia [2]. CMS patients often also display increased pulmonary artery pressure that is thought to contribute to exercise intolerance and right heart failure, which is common in these patients [3, 4]. There is, however, little information on the extent of the increase of pulmonary artery pressure in CMS.

The advent of echocardiography as a reliable tool to noninvasively estimate and compare pulmonary artery pressure (PAP) between groups [5-7] allowed eliminating the restrictions related to the more precise, but invasive and often unavailable, gold standard measurements by right heart catheterization and permitted investigators to perform studies under field conditions. Since these studies generally comprise relatively few participants, the prevalence of PAP in high-altitude dwellers suffering from CMS remains ill-defined at present.

To fill this gap, we systematically reviewed and meta-analysed all data published in English or Spanish on echocardiographic estimations of PAP and measurements of arterial oxygen saturation (SaO<sub>2</sub>) in high-altitude dwellers (>2500 m) suffering from CMS. Moreover, since there is evidence that in patients with CMS mild exercise during daily activities worsens pulmonary hypertension and contributes to the symptoms and

long-term complications [3, 8] we also analysed echocardiographic studies of PAP and arterial oxygen saturation during mild exercise in patients with CMS and high-altitude dwellers.

## MATERIALS AND METHODS

We conducted a systematic review and meta-analysis of studies reporting echocardiographic estimates of PAP and arterial oxygen saturation in CMS patients at rest and during exercise. Reviewing and reporting were performed according to the recommendations of Cochrane collaboration [9] and the PRISMA Statement [10] (see, Appendix 1, Table S1), respectively.

### Data Sources and Searches

We searched the MEDLINE and EMBASE databases up to June 2018, using PubMed and Ovid platforms. We used free text words and specific thesaurus terms (MeSH in MEDLINE and Emtree in EMBASE), including “pulmonary artery”, “pressure”, “altitude” and “altitude sickness”. We also examined the bibliographies of relevant articles to identify eligible studies missed by the database searches. (see Appendix 1)

### Study Selection

We included articles that reported the mean value and standard deviation (or standard error) of PAP by Doppler echocardiography in patients with CMS, defined as erythrocytosis with haemoglobin concentration  $>21$  g/dL in the presence of a normal pulmonary function and no history of working in the mining industry. We excluded small studies reporting data in  $<10$  participants, case reports and studies reporting duplicate

data. We first checked the abstracts of retrieved articles for eligibility and excluded ineligible studies at this stage. We then examined the full text of potentially eligible articles and depending on whether they met eligibility criteria or not, included or excluded articles.

## Data Extraction

Two reviewers (RS, NB) extracted data, using a data extraction sheet developed and piloted for this review. The two reviewers extracted the mean, standard deviation (SD) or standard error (SE) of systolic PAP and, if reported, the mean, SD or SE of arterial oxygen saturation. In the five studies that also reported PAP and arterial oxygen saturation during mild exercise [3, 4, 8, 11, 12], data for CMS patients and (for comparison) for high-altitude dwellers were extracted.

We used the right-ventricular-to-atrial pressure gradients as an estimate of systolic PAP. In most included studies, PAP derives from continuous wave Doppler sampling of the tricuspid regurgitation jet, using the simplified Bernoulli equation. In a few studies that reported mean PAP instead of systolic PAP, we used the following formula [13] to calculate systolic PAP:

$$\text{Systolic PAP} = (\text{mean PAP} \times 2) + 0.61.$$

If atrial pressure had been added to the pressure gradient, we subtracted these estimates to obtain a comparable set of data for meta-analysis.



In the study were cardiac output (CO) during exercise at 50 Watts was not directly reported, we calculated it according to the following formula:

$$\text{CO [L/min.]} = \text{stroke volume [ml]} \times \text{heart rate [bpm]} / 1000.$$

Cardiac index (CI, L/min/m<sup>2</sup>) was calculated according to the following formula:

$$\text{CO} / \text{body surface area [m}^2\text{]}$$
 and pulmonary vascular resistance (PVR) was calculated using the following formula: 
$$\text{PVR} = (\text{mPAP} - \text{PAWP}) / \text{CO}$$
, where pulmonary artery wedge pressure (PAWP) was estimated by left atrial pressure (LAP).

We further extracted bibliographic details, the study location and its altitude, the number, gender, age and ethnicity of the study participants, and the number of participants excluded from the analysis. Discrepancies between the two reviewers were resolved by discussion and consultation with the senior authors (ME, US or SFR).

### Methodological and Reporting Quality

We assessed methodological and reporting quality of studies using the following criteria:

(i) Was recruitment procedure described?; (ii) Clear description of inclusion and exclusion criteria; (iii) Number of participants with missing data for variables of interest; (iv) Was the study population representative for the general population?; (v) Was the echocardiography performed according to established standards?; (vi) Were potential sources of bias addressed?

### Statistical Analysis

We combined the data on systolic PAP and arterial oxygen saturation using random-effects meta-analysis. We converted SD to SE by dividing the SD by the square root of the number of participants included in the analysis and expressed results as mean values and 95% confidence intervals. We used univariate meta-regression models to identify factors that may have influenced PAP in people suffering from CMS. We included age, study altitude, arterial oxygen saturation, body mass index, and hemoglobin. We assessed heterogeneity between studies using the  $I^2$  statistic and the  $\text{Chi}^2$  test. We used the statistical package STATA (version 11.2, Stata Corp., College Station, TX, USA) for all analyses.

For the simulated distribution, we plotted normal distributions of systolic PAP and oxygen saturation at rest and during exercise for hypothetical populations with and without CMS, based on means and standard deviations of reported data.

## RESULTS

### *Identification of Eligible Studies*

We identified a total of 267 articles. Figure 1 shows the flow of the selection of studies and the reasons for exclusion.

Based on titles and abstracts we excluded 68 duplicates and 180 articles that did not meet inclusion criteria. We examined 19 full-text articles and excluded ten articles because they did not meet the inclusion criteria (<10 participants, comorbidities, high-altitude exposure <1 yr).

### *Characteristics of Included Studies*

Nine studies with a total of 262 participants, fulfilled the inclusion criteria. The mean age of the participants was 47 years and their number ranged from 55 participants [14] in the largest to 12 [15] in the smallest study (Table 1). All studies were performed between 3,600 and 4,350 m in the Andes. All participants were men and had an indigenous Andean (Aymara or Quechua) background. Five studies, in addition to reporting data at rest also reported measurements during mild exercise. CMS patients and high-altitude dwellers were matched for age, socio-economic background and ethnicity.

### *Methodological and Reporting Quality*

All studies provided a clear description of the eligibility criteria but due to missing or incomplete reporting, it was unclear whether participants were truly representative of the general CMS population. In all studies, echocardiography was performed according to the quality criteria of the European Association of Echocardiography [16] . Some, but not all studies addressed potential sources of bias (Table 2).

Two studies reported a selection bias towards the inclusion of patients with mild to moderate disease [3, 14]. This may have resulted in an underestimation of the true magnitude of pulmonary hypertension and arterial oxygen desaturation in the present meta-analysis. One study used the same absolute workload for exercise in all participants and did not use a subjective assessment of exercise intensity [4]. Even though the percentage of the maximal heart rate during exercise was similar in CMS patients and controls, the possibility exists that differences in relative workload may have contributed to the large differences of exercise-induced pulmonary hypertension (and pulmonary interstitial fluid accumulation) between the two groups. Finally, in one study, haemoglobin concentration was slightly  $<21$  g/l in some patients, because of bloodletting shortly before the time of study [11]. It is unlikely that the slightly lower haemoglobin

concentrations altered pulmonary artery pressure, since isovolemic hemodilution has no detectable effect on vascular function in CMS patients [17].

#### *Meta-analysis of PAP and Arterial Oxygen Saturation at rest*

In all studies, experienced echocardiographers performed the PAP measurements. The point estimate from meta-analysis of the mean systolic PAP at rest was 28 mmHg [95% confidence interval (CI) 26.28, 29.64] (Figure.2), with the reported mean values ranging from 25.0 to 34.3 mmHg. The point estimate of mean arterial oxygen saturation at rest was 84.3% [95% CI 82.9, 85.6] (Figure.3) and the reported mean values ranged from 81.0% to 87.0%. Meta-regression analyses revealed positive relationships between PAP and study altitude ( $P=0.005$ ) and haemoglobin ( $P=0.001$ ) and a negative correlation between PAP and arterial oxygen saturation ( $P=0.005$ ). No significant relationships existed between PAP and age ( $P=0.56$ ) or body mass index ( $P=0.98$ ).

#### *Meta-analysis of PAP and Arterial Oxygen Saturation during mild exercise (50W)*

Five studies also reported data on systolic PAP and arterial oxygen saturation (Figure 4) during mild exercise (50 W) in CMS patients (n=142) and high-altitude dwellers (n=125). The exercise-induced increase of PAP was almost 2-fold larger in CMS patients than in high-altitude dwellers (22.0 vs. 13.0 mm Hg,  $P=0.001$ , CMS vs controls). The point estimate of systolic PAP during mild exercise in CMS patients was significantly

( $P=0.001$ ) higher [48.26 mmHg, 95% (CI) 44.76, 51.76] than in high-altitude dwellers [36.26 mm Hg, 95% (CI) 32.99, 39.53]. Average systolic PAP during mild exercise ranged from 45.0 to 56.6 mm Hg in CMS patients and from 33.0 to 39.8 mm Hg in high-altitude dwellers. The point estimate of arterial oxygen saturation during exercise was considerably lower ( $P=0.0004$ ) in CMS patients [82.1%, 95% (CI) 80.6, 83.7] than in controls [89.4%, 95% (CI) 88.5, 90.3], and its mean values ranged from 79.0 to 84.9% in the patients and from 87.7 to 90.3% in the controls.

Cardiac output during mild exercise was comparable in CMS patients and controls ( $9.4\pm1.1$  vs.  $9.2\pm0.9$  L/min,  $p=0.80$ ) whereas left atrial pressure was slightly, albeit significantly higher in the patients ( $10.1\pm0.7$  vs.  $9.2\pm0.3$  mm Hg,  $p=0.0457$ ). Calculated pulmonary vascular resistance at 50 W tended to be higher in the patients ( $2.7\pm0.3$  vs.  $2.2\pm0.6$  mm Hg/L/min,  $p=0.090$ ), a tendency which disappeared after correction for the increased hematocrit according to reference [18].

In all meta-analyses the heterogeneity was between 60 and 85 %, which in all cases was significant ( $p$ -values between 0.04 and 0.0001).

*Simulated distribution of PAP and arterial oxygen saturation in CMS patients and high-altitude dwellers.*

Figure 5 and 6 show simulated distribution curves of PAP and arterial oxygen saturation in CMS patients and high-altitude dwellers at rest and during mild exercise. Curves are shifted towards higher (PAP), respectively lower (arterial oxygen saturation) values in the patients.

## DISCUSSION

Among the more than 140 million people living at high altitude, CMS represents a major health problem. In the Andes 5 to 10% of high-altitude dwellers suffer from this debilitating disease which is often associated with increased PAP that is thought to lead to substantial morbidity and mortality [1, 2]. However, the extent of this increase remains poorly defined. To provide such information, we performed a meta-analysis on echocardiographic estimations of PAP and arterial oxygen saturation 287 high-altitude dwellers suffering from CMS. Since PAP measurements at rest underestimate the values observed during daily activity [8], we also searched for measurements of PAP during mild exercise in the meta-analysed studies. [19]. The meta-analysis revealed mean systolic PAP and mean arterial oxygen saturation are roughly 11% higher and 7% lower, respectively, than those meta-analysed previously in high-altitude dwellers living at similar altitude. Mild exercise strikingly accentuates the differences of PAP and arterial oxygen desaturation between the two groups. Taken together, these findings suggest that in CMS patients the PAP increase appears sufficiently severe to cause symptoms and long-term sequels.

The present data represent by far the largest dataset on PAP and arterial oxygen saturation in patients suffering from CMS. Echocardiography is the standard technique to assess PAP in high-altitude populations, since for ethical and logistic reasons invasive measurements are not feasible in population-based studies [19]. Echocardiographic estimations of PAP have been validated against invasive measurements at high altitude [5] with good agreement between invasive and non-invasive measurements [6, 20]. Moreover, agreement between echocardiographic and invasive measures of pulmonary pressures during exercise is good among patients with a high quality tricuspid regurgitation Doppler signal [21]. Finally, the accuracy of echocardiographic estimations of PAP may depend on the experience of the echocardiographer. It is important to note that experienced investigators having published extensively in the field performed the estimations of PAP in all the studies meta-analysed [13, 22-24]. Taking the current definitions of pulmonary hypertension as a mean PAP >25 (European Respiratory Society) [25] or >30 mmHg (high-altitude consensus) [2] the findings of our meta-analysis (systolic PAP of 27.9 = mean PAP of 22 mmHg) indicate that in CMS patients living at high altitude (3,600-4,200 m) pulmonary hypertension at rest is rare.

The high-altitude Consensus [2] states that this limit holds true in the absence of excessive erythrocytosis, implying that an increased haematocrit may be a cause of falsely diagnosed pulmonary hypertension [26]. This effect, which could contribute to differences in pulmonary artery pressure between high-altitude populations showing different erythropoietic responses to ambient hypoxia, has however never been systematically quantified. Along the same lines, the effects of blood-letting as treatment of increased pulmonary artery pressure in CMS are controversial [27-31] and need to be re-examined in controlled prospective studies.



An important strength of the present study is that we also meta-analysed PAP during exercise. There is evidence that PAP measurements at rest may greatly underestimate PAP values during daily activity in CMS patients. In turn, this might underestimate the potential consequences of increased PAP for long-term morbidity and mortality in this population [8]. To provide information on this important issue, we included in our meta-analysis studies assessing PAP during mild exercise (50 W), which will be associated with many activities of daily living. Of note, all exercise studies were performed in the semi-recumbent position, a procedure suitable to obtain reliable and reproducible tricuspid regurgitation envelopes during exercise [7].

During mild exercise, the difference in mean systolic PAP between CMS patients and high-altitude dwellers was markedly greater (48.3 vs. 36.3 mm Hg) than the one meta-analysed previously at rest (28.0 vs. 25.0 mm Hg, CMS vs. controls) [19]. Indeed, in CMS patients mean PAP during mild exercise at 50 W (34.5 mm Hg, 95% CI, 32.4, 36.6) is above the recently suggested definition of exercise-induced pulmonary hypertension (mean PAP >30 mm Hg) [32], whereas in high-altitude dwellers mean PAP remains below this suggested cut-off value (27.2 mm Hg 95% CI 25.2, 29.2). There is consensus emerging to define exercise-induced pulmonary hypertension by a mean PAP >30 mm Hg at a cardiac output <10 L/min and a total pulmonary resistance >3 Wood units, in the absence of pulmonary hypertension at rest [32]. The present meta-analysis demonstrates that CMS patients fulfil two of these three criteria already at mild exercise. It is likely that many of them will fulfil all three criteria at maximal exercise. In line with this speculation, in the study of Groepenhoff et al. [33], we estimated a pulmonary vascular resistance of roughly 3.7 Wood units in CMS patients at maximal exercise.

Of note, in disease states predisposing to pulmonary hypertension, exercise-induced pulmonary hypertension is a well-established cause of decreased exercise capacity, precedes the development of manifest pulmonary hypertension at rest in a proportion of patients and is associated with decreased life expectancy [32]. Several mechanisms may increase PAP in CMS. Pulmonary resistive vessels are less distensible in CMS patients than in healthy highlanders, probably because of vascular remodeling [8, 33], which is also detectable in the systemic circulation [17]. Moreover, exaggerated sympathetic activation [34] in conjunction with increased oxidative-nitrosative stress and decreased nitric oxide bioavailability [35, 36] may also facilitate pulmonary vasoconstriction. Finally, exercise-induced arterial oxygen desaturation was considerably more severe in the patients than in the control subjects (82.1 vs. 89.4 %).

Collectively, these data strengthen the concept that in patients with CMS, measurements at rest markedly underestimate pulmonary hypertension and arterial oxygen desaturation during daytime activity. Interestingly, recent data show that sleep disordered breathing and nocturnal hypoxemia are more severe in CMS patients than in control subjects [12] and associated with pulmonary vascular dysfunction. It appears therefore possible that daytime measurements of PAP at rest also underestimate differences in PAP between CMS and high-altitude dwellers during sleep. In line with this speculation, invasive measurements of PAP in patients with obstructive sleep apnoea showed a marked progressive increase of PAP during the night [37].

All studies meta-analysed here were performed in Andean high-altitude dwellers. This may be related, at least in part, to the fact that the prevalence of CMS appears to be considerably higher in Andean than in Tibetan or African high-altitude dwellers [38]. Genetic studies provide evidence for differences in the evolutionary adaptation to high altitude between Andean, Tibetan and Ethiopian high-altitude populations [39]. These differences may have resulted in different regulation of the pulmonary circulation and may contribute to differences in PAP between high-altitude populations. It would be important to assess PAP in CMS patients of other than Andean origin.

We used meta-regression models to identify factors that may have influenced PAP in CMS patients. We found that significant positive relationships existed between PAP and study altitude and haemoglobin concentration. Moreover, a significant negative relationship existed between PAP and arterial oxygen saturation. The significant relationship between study altitude and PAP (and arterial O<sub>2</sub> saturation) also indicates that differences in study altitude explain, at least in part, the heterogeneity of the studies meta-analysed. Other reasons for the heterogeneity might be differences in CMS severity between studies or other unreported differences between study populations.

The present data represent by far the largest dataset on PAP and arterial oxygen saturation at rest and during mild exercise in patients with CMS and high-altitude dwellers. However, the number of subjects remains relatively small and is limited to Andeans. Additional studies assessing PAP and arterial oxygen saturation at rest and during mild exercise in CMS patients living in the Andes and, importantly, in other high-altitude regions of the world, are urgently needed. Finally, one should keep in mind that echocardiographic measurements of PAP, while highly accurate for population studies,

are inappropriate for diagnostic decisions in individuals, because of their lack of precision.

To conclude, this is the first systematic review and meta-analysis of studies reporting echocardiographic estimates of PAP and measurements of arterial oxygen saturation in high-altitude dwellers suffering from CMS. The data indicate that in CMS patients, mean systolic PAP at rest is roughly 3 mm Hg higher and arterial oxygen saturation 6 % lower than the values previously meta-analysed in high-altitude dwellers [19], but PAP at rest does not fulfil the current criteria for pulmonary hypertension. Importantly, mild exercise expected to be frequently associated with daily activity markedly accentuates the difference in PAP between patients and controls. Exercise-induced pulmonary hypertension may cause symptoms and long-term sequelae in high altitude dwellers.

The exaggerated increase of PAP during exercise induces interstitial fluid accumulation in the lung [4] and may represent a cause of exertional dyspnea frequently encountered in CMS patients. Moreover, exercise-induced pulmonary hypertension, however measured, has been shown to be of diagnostic and/or prognostic relevance in mitral valve disease [40], aortic stenosis [41], heart failure [42], systemic sclerosis [43-45], chronic obstructive pulmonary disease [46] and symptomatic patients after pulmonary endarterectomy [47]. Prospective studies are urgently needed examining whether similar long-term sequelae are present CMS patients.

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## DISCLOSURES

All authors have read and approved the manuscript. This material has not been reported previously except as an abstract and is not under consideration for publication elsewhere. The authors declare that they have no financial or other conflicts of interest.

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**Table 1.** Characteristics of included studies

First author (year)	No. of Participants*	Mean (SD) age (years)	Mean (SD) Hb (g/dL)	Mean (SD) Htco (%)	Study location (country)	Altitude (m)	Ethnicity
Vargas (2006)[48]	30	22.3 (4.3)	19.5 (0.7)	-	La Paz - Bolivia	3600	Aymara
	28	46.7 (7.1)	24 (2.3)	-	La Paz - Bolivia	3600	Aymara
Maignan (2009)[14]	55	45 (10)	23.1 (1.6)	-	Cerro Pasco - Perú	4300	Quechua
Stuber (2010)[8]	30	47 (13)	21.5 (1.7)	66	La Paz, El Alto - Bolivia	3600	Aymara
Pratali (2012)[4]	15	54 (9)	21.7 (1.3)	66	La Paz - Bolivia	3600	Aymara
Groepenhoff (2012)[33]	13	50 (10.8)	24 (3.6)	-	Cerro Pasco - Perú	4350	Quechua
Pratali (2013)[3]	46	51 (10)	21.5 (2)	63.3	La Paz - Bolivia	3600	Aymara
Dedobbeleer (2015)[15]	12	51 (10)	24 (2)	-	Cerro Pasco - Perú	4350	Quechua
Brenner (2015)[11]	35	52.4 (11.9)	21.6 (2.1)	62.5	La Paz - Bolivia	3600	Aymara
Rexhaj (2016)[12]	23	52.8 (9.8)	21.7 (1.3)	66.9	La Paz - Bolivia	3600	Aymara

\* All participant are men; Hb = Hemoglobin; Htco = Hematocrit.

**Table 2.** Assessment of methodological quality of included studies

<b>Study</b>	<b>Was recruitment procedure described?</b>	<b>Clear description of inclusion/exclusion criteria</b>	<b>Number of participants with missing data for variables of interest (%)</b>	<b>Was the study population representative for the general population?</b>	<b>Was Echocardiography perform reliably?</b>	<b>Were potential sources of bias addressed?</b>
Vargas 2006	no	yes	unclear	unclear	yes	no
Maignan 2009	no	yes	18 (32)	unclear	yes	yes
Stuber 2010	no	yes	1 (3.3)	unclear	yes	yes
Pratali 2012	no	yes	unclear	unclear	yes	yes
Groepenhoff 2012	no	yes	unclear	unclear	yes	no
Pratali 2013	yes	yes	3 (6.5)	unclear	yes	yes
Dedobbeleer 2015	no	yes	unclear	unclear	yes	no
Brenner 2015	yes	yes	unclear	unclear	yes	unclear
Rexhaj 2016	unclear	yes	3 (13)	unclear	yes	no

FIGURE LEGEND

**Figure 1.** Flow of information through the different phases of systematic review. *n*, Number of the studies.

**Figure 2.** Meta-analysis of mean systolic pulmonary artery pressure at rest and its 95% confidence interval (CI) in high-altitude dwellers suffering from CMS.

**Figure 3.** Meta-analysis of mean arterial oxygen saturation at rest and its 95% CI in CMS patients.

**Figure 4.** Meta-analysis of mean systolic pulmonary artery pressure and mean arterial oxygen saturation during mild exercise (50W) and their 95% confidence interval (CI) in high-altitude dwellers (Panels A and C) and CMS patients (panels B and D).

**Figure 5.** Predicted distribution of mean systolic pulmonary artery pressure in high-altitude dwellers and CMS patients, at rest and during mild exercise.

**Figure 6.** Predicted distribution of mean arterial oxygen saturation in high-altitude dwellers and CMS patients, at rest and during mild exercise.

## Appendix 1

**Table S1.** PRISMA checklist

Section/topic	#	Checklist item	Reported on page #
<b>TITLE</b>			
Title	1	Identify the report as a systematic review, meta-analysis, or both.	1
<b>ABSTRACT</b>			
Structured summary	2	Provide a structured summary including, as applicable: background; objectives; data sources; study eligibility criteria, participants, and interventions; study appraisal and synthesis methods; results; limitations; conclusions and implications of key findings; systematic review registration number.	3
<b>INTRODUCTION</b>			
Rationale	3	Describe the rationale for the review in the context of what is already known.	4
Objectives	4	Provide an explicit statement of questions being addressed with reference to participants, interventions, comparisons, outcomes, and study design (PICOS).	4-5
<b>METHODS</b>			
Protocol and registration	5	Indicate if a review protocol exists, if and where it can be accessed (e.g., Web address), and, if available, provide registration information including registration number.	-
Eligibility criteria	6	Specify study characteristics (e.g., PICOS, length of follow-up) and report characteristics (e.g., years considered, language, publication status) used as criteria for eligibility, giving rationale.	5-6
Information sources	7	Describe all information sources (e.g., databases with dates of coverage, contact with study authors to identify additional studies) in the search and date last searched.	5
Search	8	Present full electronic search strategy for at least one database, including any limits used, such that it could be repeated.	Appendix 1, Table S1
Study selection	9	State the process for selecting studies (i.e., screening, eligibility, included in systematic review, and, if applicable, included in the meta-analysis).	5-6
Data collection process	10	Describe method of data extraction from reports (e.g., piloted forms, independently, in duplicate) and any processes for obtaining and confirming data from investigators.	6-7
Data items	11	List and define all variables for which data were sought (e.g., PICOS, funding sources) and any assumptions and simplifications made.	7
Risk of bias in individual studies	12	Describe methods used for assessing risk of bias of individual studies (including specification of whether this was done at the study or outcome level), and how this information is to be used in any data synthesis.	7
Summary measures	13	State the principal summary measures (e.g., risk ratio, difference in means).	7-8

Synthesis of results	14	Describe the methods of handling data and combining results of studies, if done, including measures of consistency (e.g., $I^2$ ) for each meta-analysis.	7-8
Risk of bias across studies	15	Specify any assessment of risk of bias that may affect the cumulative evidence (e.g., publication bias, selective reporting within studies).	-
Additional analyses	16	Describe methods of additional analyses (e.g., sensitivity or subgroup analyses, meta-regression), if done, indicating which were pre-specified.	8
<b>RESULTS</b>			
Study selection	17	Give numbers of studies screened, assessed for eligibility, and included in the review, with reasons for exclusions at each stage, ideally with a flow diagram.	8 - Figure 1
Study characteristics	18	For each study, present characteristics for which data were extracted (e.g., study size, PICOS, follow-up period) and provide the citations.	8-9, 22 Table 1
Risk of bias within studies	19	Present data on risk of bias of each study and, if available, any outcome level assessment (see item 12).	9, 23 Table 2
Results of individual studies	20	For all outcomes considered (benefits or harms), present, for each study: (a) simple summary data for each intervention group (b) effect estimates and confidence intervals, ideally with a forest plot.	-
Synthesis of results	21	Present the main results of the review. If meta-analyses are done, include for each, confidence intervals and measures of consistency.	10-11 Figures 2, 3, 4
Risk of bias across studies	22	Present results of any assessment of risk of bias across studies (see Item 15).	-
Additional analysis	23	Give results of additional analyses, if done (e.g., sensitivity or subgroup analyses, meta-regression [see Item 16]).	11 Figure 5
<b>DISCUSSION</b>			
Summary of evidence	24	Summarize the main findings including the strength of evidence for each main outcome; consider their relevance to key groups (e.g., healthcare providers, users, and policy makers).	11-14
Limitations	25	Discuss limitations at study and outcome level (e.g., risk of bias), and at review-level (e.g., incomplete retrieval of identified research, reporting bias).	14-15
Conclusions	26	Provide a general interpretation of the results in the context of other evidence, and implications for future research.	15
<b>FUNDING</b>			
Funding	27	Describe sources of funding for the systematic review and other support (e.g., supply of data); role of funders for the systematic review.	16

From: Moher D, Liberati A, Tetzlaff J, Altman DG, The PRISMA Group (2009). Preferred Reporting Items for Systematic Reviews and Meta-Analyses: The PRISMA Statement. PLoS Med 6(7): e1000097. doi:10.1371/journal.pmed1000097

## Search Strategy

We ran the following search strategy in **PubMed** until June 2018:

1. "pulmonary artery" [MeSH Terms]  
OR
2. "pulmonary artery" [All Fields]  
OR
3. "pulmonary" [All Fields] AND "artery" [All Fields]  
OR
4. "pulmonary artery" [Title/Abstract]
5. 1 OR 2 OR 3 OR 4
6. "blood pressure" [MeSH Terms]  
OR
7. "blood pressure" [All Fields]  
OR
8. "pressure" [MeSH Terms]  
OR
9. "pressure" [All Fields]
10. 6 OR 7 OR 8 OR 9
11. 5 AND 10
12. "pulmonary hypertension" [MeSH Terms]  
OR
13. "pulmonary hypertension" [All Fields]  
OR
14. "pulmonary hypertension" [Title/Abstract]
15. 12 OR 13 OR 14
16. 11 OR 15
17. "chronic" [All Fields]  
OR
18. "chronic" [Title/Abstract]
19. 17 OR 18
20. "altitude sickness" [MeSH Terms]  
OR
21. "altitude sickness" [All Fields]  
OR
22. "altitude" [All Fields] AND "sickness" [All Fields]  
OR
23. "altitude sickness" [Title/Abstract]  
OR
24. "mountain sickness" [All Fields]  
OR
25. "mountain" [All Fields] AND "sickness" [All Fields]  
OR
26. "mountain sickness" [Title/Abstract]
27. 20 OR 21 OR 22 OR 23 OR 24 OR 25 OR 26

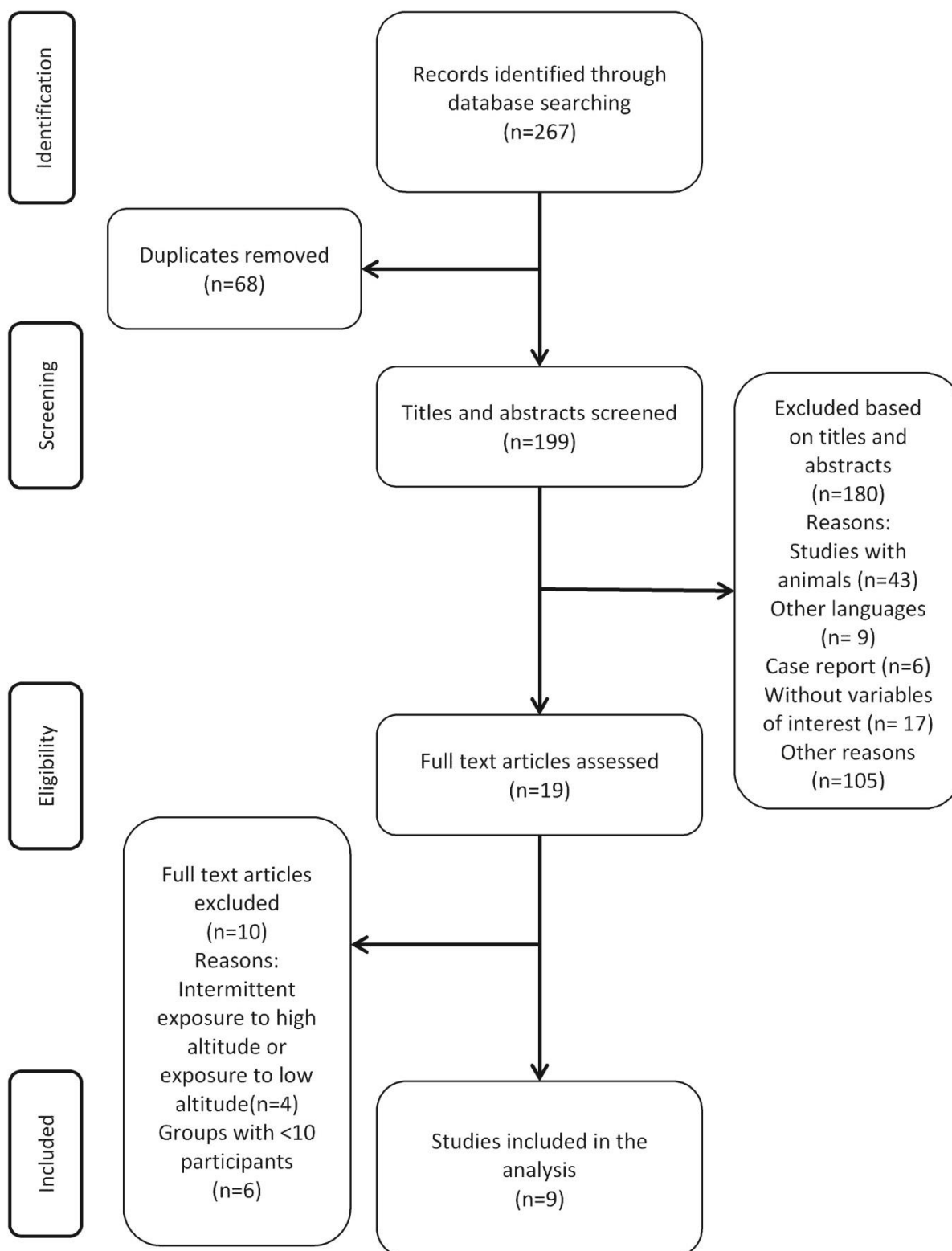


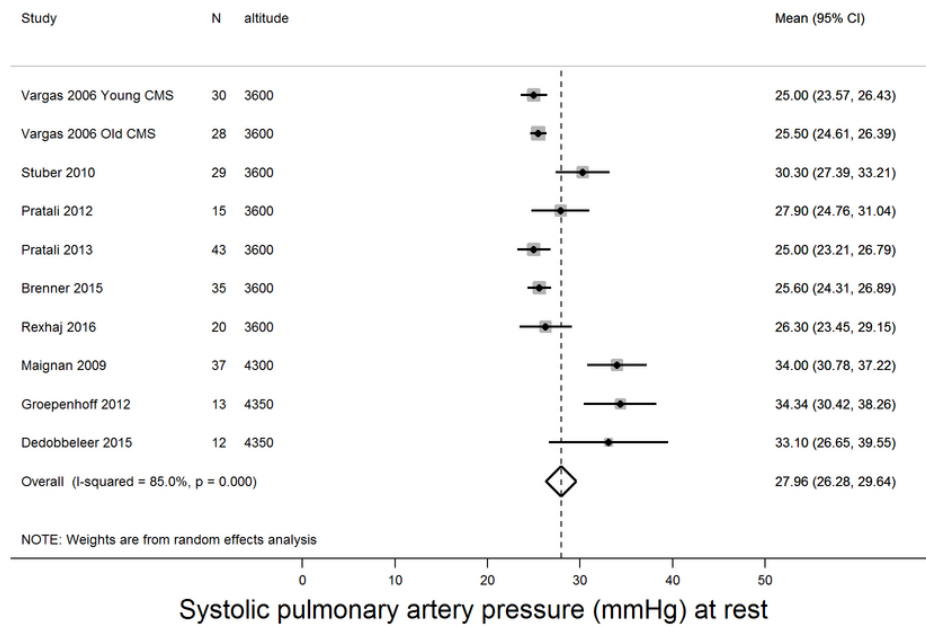
28. 19 AND 27

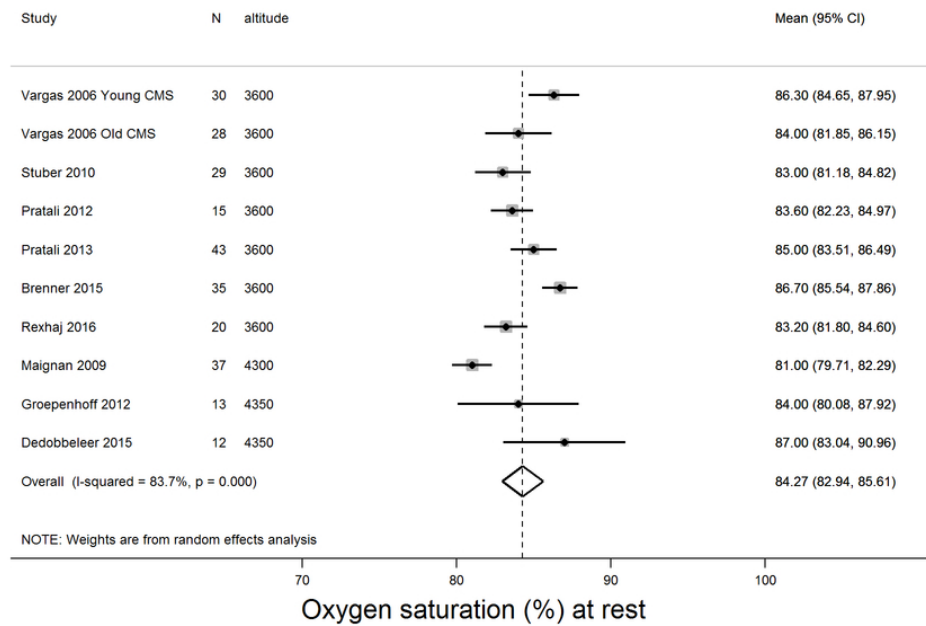
29. 16 AND 28

We ran the following search strategy in **EMBASE** until June 2018:

1. chronic mp.
2. altitude sickness mp. or exp altitude disease/
3. mountain sickness mp.
4. chronic mountain sickness mp.
5. monge's disease mp.
6. 1 and 2
7. 1 and 3
8. 4 or 5 or 6 or 7
9. exp lung artery pressure/ or lung artery pressure mp. or exp pulmonary artery/
10. pulmonary hypertension mp. or exp pulmonary hypertension/
11. systolic pulmonary artery mp.
12. elevated pulmonary artery pressure mp
13. 9 or 10 or 11 or 12
14. high altitude mp. or exp altitude/
15. 8 and 13 and 14

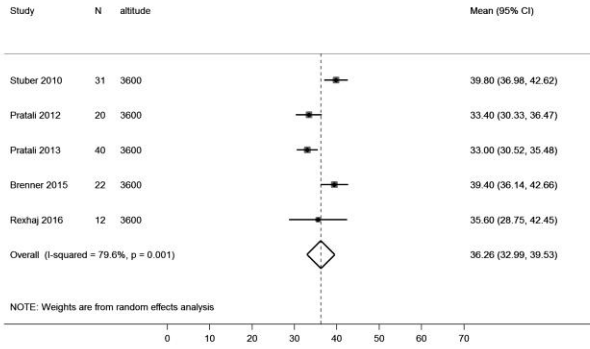






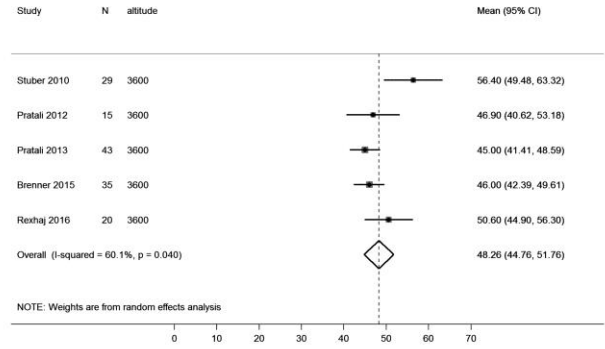
A

CONTROL



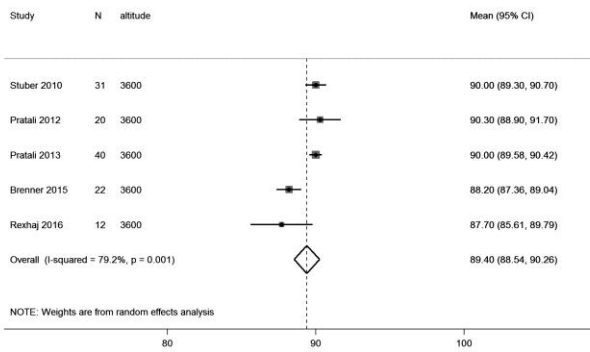
B

CMS

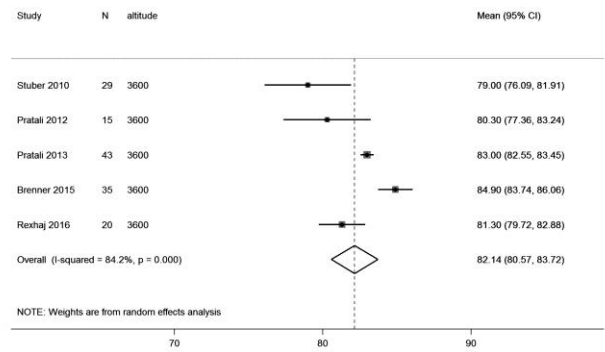


Systolic Pulmonary Artery Pressure (mmHg)  
During 50 W Exercise

C



D



Arterial Oxygen Saturation (%)  
During 50 W Exercise

